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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/796,160	03/10/2004	Franz-Josef Rubroeder	DEAV1999/L042USCNT1	2543
5487	7590	06/09/2008		
ANDREA Q. RYAN SANOFI-AVENTIS U.S. LLC 1041 ROUTE 202-206 MAIL CODE: D303A BRIDGEWATER, NJ 08807			EXAMINER CHANDRA, GYAN	
			ART UNIT 1646	PAPER NUMBER
			NOTIFICATION DATE 06/09/2008	DELIVERY MODE ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/796,160	<b>Applicant(s)</b> RUBROEDER ET AL.	
	<b>Examiner</b> GYAN CHANDRA	<b>Art Unit</b> 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 23-69 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 23-65, 68 and 69 is/are rejected.
- 7) ☒ Claim(s) 66 and 67 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

In view of the Appeal Brief filed on 4/30/2008, PROSECUTION IS HEREBY REOPENED. Anew ground of rejection is set forth below.

The finality of the Office Action mailed on 3/7/2007 is withdrawn to include new references to support the rejections under 35 USC § 102 (b) and 35 USC § 103 (a).

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing this office action.

Applicants' filing of a Terminal Disclaimer on 3/10/2008 is acknowledged. The TD has been approved.

### **Status of Application, Amendments, And/Or Claims**

Claims 23-69 are pending and under examination.

### ***Claim Objections***

Claims 40, 43-49, 58 and 65 objected to because of the following informalities:

Claim 40 has a typographical error which has a “,” at the end of the claim and should be replaced with “.”

Claim 43 recites the term “far the storage” which should be replaced with “for the storage”

Claims 43-47 recite the term “a period of” which should be replaced with “a storage period of”

Claims 58 and 65, misspelled the word “renaturatlon” which should be “renaturation”

Appropriate correction is required.

### **Double Patenting-withdrawn**

The rejection of claims 23-69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6, 339,061, is withdrawn in view of Applicant's submission TD on 3/10/2008 and which has been approved.

However, upon further consideration of new search results, a new ground(s) of rejection is made as set forth below.

### **New Ground of Rejections**

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 23 recites the phrase "the effective concentration" renders the claim(s) indefinite because it is unclear which "effective concentration" is being drawn to. Therefore, the metes and the bounds of the claim cannot be determined.

Claims 24-31, 33-39, 41-42 are rejected for being directly or indirectly dependent from a broad and indefinite claim (i.e., claim 23).

Claims 32, 40, 57 and 65 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: (i) in claims 32 and 57, the method steps are directed to a protein encoded by an expression vector, which is not complete in it self as an expression vector is designed to express a protein encoded by a nucleic acid sequence. Applicants may amend the claims to include "comprising a polynucleotide encoding the protein".

(ii) in claims 40 and 65, the methods recite " further comprising the renaturation of the heterologous protein" from the previous claim. But the previous claims recite

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“optional disruption of the microorganism” (e.g., claim 39 or 64), and in this case if the microorganism is not disrupted then proteins would not be denatured. Therefore, one of the skill in the art would not know how to practice the instant invention.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

**For the purpose of comparing the claims with the prior art, it is noted that “the effective concentration does not decrease” is being interpreted as “the effective concentration of protein does not decrease”**

Claims 23-24, 33-37, 43-49, 58-62, are rejected under 35 U.S.C. 102(b) as being anticipated by Ho et al (US Patent No. 5,780,431).

The instant claims are drawn to a process for the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease on the effective concentration of the protein by reducing chemical modification of SH groups on the protein during a period of greater than 24 hours 48

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hours, 1 week, 2 weeks, 4 weeks, 2 months or more (claim 43-49) , wherein the effective concentration does not decrease by more than about 7% (claim 23), wherein the effective concentration does not decrease by 3%, wherein the protein is a heterologous protein produced in an organism (claim 24), wherein the protein is present in dissolved form (claim 33,58), wherein the protein is present in suspension (claims 34, 59), wherein the storage of protein takes place at about 0° C to about 50° C (claim 60), wherein the storage of protein takes place at about 0° C to about 30° C (claim 61), and wherein the storage of protein takes place at about 5° C (claim 62).

Ho et al teach a method for enhancing the stability of corticotropin releasing factor (CRF) protein in a formulation comprising an amino acid selected from the group consisting of methionine, arginine,.. and cysteine and wherein in the concentration of an amino acid ranges from 1-100 mM (see claims 24, 25, 36 and 37). Ho et al teach that the formulations (or compositions) are stable when stored at about 2° C-8° C for 24 months (column 9, lines 1+), which encompasses the time limitations such greater than 24 hours, 48 hours, 1 week, 2 weeks, 4 weeks, 2 months or more as recited in claims 43-49 of the instant invention. Further, the teachings of Ho anticipates the limitations for storing a protein at temperature such as 0° C to about 50° C; 0° C to about 30° C or at about 5° C because Ho et al teach storing a protein composition between 2° C-8° C (col. 9, lines 1+). Ho et al teach preparing a composition comprising CRF in a buffer and states that various formulations can be prepared as known to one of the skill in the art (column 6, 24+). They teach that liquid formulations can be prepared with an osmolarity which is approximately physiological (col. 7, lines 30+). Ho et al do not explicitly teach

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the effective concentration of protein does not decrease by about 7% or about 3%.

However, the prior art of record implicitly anticipates the instant invention. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See *Bristol-Myers Squibb Company v. Ben Venue Laboratories* 58 USPQ2d 1508 (CAFC 2001).

Hence, even though the claims are drawn to a mechanism by which the effective concentration of a protein does not decrease by about 7% or about 3%, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In *re Wiseman*, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In *re Baxter Travenol Labs*, 21 USPQ2d 1281 (Fed. Cir. 1991). See *M.P.E.P.* 2145.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.



The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 25-32, 39-40, 50-57, 64-65 and 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ho et al as applied to claims 23-24, 33-37, 43-49, and 58-62 above, and further in view of Eaton et al (5, 830,647).

The instant claims are further drawn to a process for the storage of a protein in an aqueous solution, comprising adding an amount of cysteine effective to delay the temporal decrease on the effective concentration of the protein by reducing chemical modification of SH groups on the protein, wherein the protein is a heterologous protein produced in an organism (claim 25, 50), wherein the organism is microorganism (claim

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68, 69), wherein the microorganism is a bacterium (claim 26, 51), wherein the bacterium is *E. coli* (27, 52), wherein said microorganism is a yeast (claim 28, 53), wherein said yeast is *P. pastoris* (claim 30, 55), wherein said yeast is *S. cerevisiae* (claim 54) wherein said protein is produced in an insect cell (claim 31, 56), and wherein said protein is encoded by an expression vector (claim 32, 57).

Eaton et al teach making a heterologous protein such as Mpl ligand (thrombopoietin) by recombinant technology which uses transforming a cDNA encoding a protein into a host cell or organism (column 23, lines 36+). They teach various vectors suitable for expressing such protein in many different host cells (col. 35-36). They teach that a host cell can be prokaryote, yeast or higher eukaryotic cells (col. 36, lines 21+). Further, they teach that prokaryotic cells can be *E. coli*, yeast, *S. cerevisiae*, or *P. pastoris* (col. 36, line 35+). Eaton et al teach that a suitable cell can be insect cells (column 36, line 58+).

Therefore, it would have been prima facie obvious to one of the ordinary skill in the art at the time of invention was made to express a heterologous protein using recombinant technology and a host cell such as *E. coli*, yeast, *S. cerevisiae*, *S. pombe* or insect cell as taught by Eaton et al. One of the skill in the art would have been motivated to do so because Eaton et al teach that a heterologous protein can be expressed various host cell as they offer different advantages and one of the skill in the art would know which cell to choose from those taught by Eaton et al. Additionally, one of the skill in the art would have a reasonable expectation of success because Eaton et al teach

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expressing a heterologous protein in various host cells using the recombinant technology.

Claims 66 and 67 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GYAN CHANDRA whose telephone number is (571)272-2922. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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/Gary B. Nickol /

Supervisory Patent Examiner, Art Unit 1646